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Sustained systemic arterial hypertension induced by extended hypobaric hypoxia

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Sustained systemic arterial hypertension induced by extended hypobaric hypoxia. Regular administration of recombinant erythropoietin (EPO) is frequently complicated by a rise in arterial blood pressure. We therefore asked if prolonged stimulation of endogenous EPO production has the same effect. To this end, male Sprague-Dawley rats were placed in a hypobaric chamber (390 mm Hg) for 24 days. The control (NL) group was placed in the chamber at normobaric condition. The animals were then removed from the chamber and monitored through day 108. Plasma EPO peaked within 24 hours and returned to baseline by day 7 and remained so thereafter. Hematocrit rose steadily during the hypoxic phase and declined steadily during the normobaric phase, reaching the baseline on day 45. This was accompanied by parallel changes in erythrocyte mass and blood volume. The rise in hematocrit during hypoxia was accompanied by a parallel rise in blood pressure which peaked on day 24. Despite the restoration of normal hematocrit, erythrocyte mass and blood volume following resumption of normoxia, blood pressure remained elevated throughout the observation period. To dissect the role of hypoxia from that of the associated rise in hematocrit, the experiments were repeated using a group of rats whose hematocrits were kept constant by repeated phlebotomies. These animals exhibited a sustained rise in blood pressure identical to that found in the original group. Thus, prolonged hypobaric hypoxia leads to a severe hematocrit-independent systemic hypertension (HTN) that persists long after the restoration of normoxia. Given the transient nature of the rise in its plasma concentration, endogenous EPO does not appear to play a role in the genesis of the observed systemic HTN. The authors believe that this animal model can be used for future studies of the mechanism, consequences and treatment of acquired HTN.

Regular administration of recombinant human erythropoietin (EPO) in patients with chronic renal failure (CRF) is frequently complicated by development of *de novo* HTN or exacerbation of pre-existing HTN [1–10]. The EPO-associated rise in arterial blood pressure usually manifests within a few weeks to months after initiation of therapy and generally subsides with its discontinuation [1–10]. The precise mechanism(s) by which EPO raises arterial blood pressure is uncertain. Increased hematocrit and a direct or indirect effect of EPO on vascular smooth muscle tone have been proposed as possible candidates [9–12].

Given the fact that regular administration of exogenous EPO can raise systemic arterial blood pressure, we hypothesized that chronic stimulation of endogenous EPO may have a similar effect. To test this hypothesis we studied rats during and after a 24-day exposure to hypobaric hypoxia. The data were compared with those obtained from a group of sham-treated rats kept in a similar environment under normobaric condition. The results showed that after an early peak, plasma EPO returned to baseline within a few days despite persistent hypoxia. However, arterial blood pressure began to rise steadily after restoration of normal plasma EPO level reaching a peak by the end of the hypoxic period and remained elevated thereafter despite restoration of normoxic condition. These observations disproved the direct role of endogenous EPO as a culprit in the pathogenesis of the observed hypoxia-induced sustained systemic HTN. However, the experiments led to identification of a model of acquired HTN that may be useful in future studies of the pathogenesis, complications and management of HTN.

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Methods

Animals

Male Sprague-Dawley rats (Charles River, Wilmington, MA, USA) weighing 270 to 300 g were used in these experiments. They were allowed free access to food (regular rat chow, Purina Mills Inc., Brentwood, MO, USA) and water throughout the study period. The animals were randomly assigned to the hypoxic (group A) and sham-treated control groups. Animals assigned to the hypoxic group were placed in a hypobaric chamber in which the air pressure was kept at 390 mm Hg using a continuous vacuum pump and an adjustable inflow valve. The interior of the chamber was maintained at the ambient temperature. A normal interior light cycle was accommodated through glass windows in the chamber's structure.

The hypoxic group was kept under hypobaric conditions for 24 days. The chamber was briefly opened thrice weekly for routine animal care, measurement of arterial blood pressure and procurement of blood samples, as appropriate. Animals randomized to the sham-treated control group were treated in an identical manner excepting normal air pressure within the chamber. After the conclusion of the 24-day exposure to hypobaric hypoxia or sham-treatment, the rats were placed in regular cages and followed through day 108. In an attempt to dissect the possible role of hypoxia from that of the associated rise in hematocrit and erythrocyte mass on arterial blood pressure, the experiments were repeated using regular phlebotomies gauged to keep the hematocrit constant (group B). This was accomplished by orbital sinus puncture (under light anesthesia) for measurement of hematocrit and blood removal as needed two to three times weekly.

Arterial blood pressure was measured using a tail sphygmomanometer (Harvard Apparatus, South Natick, MA, USA) at baseline (day 0) and on days 1, 3, 7, 14, 24, 25, 31, 45, 66 and 108. Blood samples were obtained by orbital sinus puncture under light anesthesia at appropriate intervals. Hematocrit, platelet count and serum creatinine were measured using standard laboratory techniques.

Plasma erythropoietin was measured by radioimmunoassay as previously described [13] using a kit purchased from Incstar Corp. (Stillwater, MN, USA).

Measurement of blood volume

Blood volume was measured on days 24 and 66 as follows. After insertion of arterial and venous catheters, the animals were injected with 0.1 ml of a radioiodinated (^{125}I) serum albumin preparation (RISA, 0.75 μCi/rat) through the venous catheter. The venous catheter was then flushed with 0.1 ml normal saline, and blood samples (0.3 ml) were obtained from the arterial line at 5, 10 and 20 minutes for determination of hematocrit and plasma radioactivity. Plasma radioactivity was determined in 0.1 ml of plasma obtained at the above internals and plotted against time using semilogarithmic paper. The plasma radioactivity at time zero was determined by extrapolation using the above curve. On each occasion, the radioactivity present in 0.1 ml of the RISA preparation was separately measured. Measurements were carried out for one minute using a gamma counter (Gamma 5500B, Beckman Inc., Irvine, CA, USA). Residual radioactivity remaining in the venous catheter was determined at the end of each experiment. The unbound ^{125}I was determined after precipitation of the plasma proteins by 10% trichloroacetic acid. The amount of albumin-bound radioactivity delivered was calculated using the following equation:

$$\text{Albumin-bound radioactivity delivered} = (\text{CPM/ml of RISA} \times \text{volume RISA injected}) - \text{CPM venous catheter} - \text{CPM unbound } ^{125}\text{I}$$

Plasma volume was calculated by dividing the above value by the plasma radioactivity concentration (CPM/ml) at time zero. Blood volume was derived from the equation:

$$\text{Blood volume} = \text{Plasma volume}/(1 - \text{hematocrit})$$

Erythrocyte mass was calculated from blood volume and hematocrit.

Endothelin determination

Plasma endothelin was measured by radioimmunoassay (RIA) using reagents obtained from Nichols Institute Diagnostics (San Juan Capistrano, CA, USA). EDTA plasma samples were extracted with acetone, and the acetone extract was dried under nitrogen (extraction efficiency was 90%). The dried extract was reconstituted and assayed in an RIA using ^{125}I-endothelin and rabbit anti-endothelin. The bound/free separation was achieved using second antibody separation procedure (donkey anti-rabbit gamma globulin). To avoid interassay variations, all samples were assayed in a single session. The intra-assay variation for this test was less than 8%. Sensitivity of the assay was 1 pg/ml for a 1 ml sample size. The specificity of the antibody was as follows: endothelin 1 to 100%, endothelin 2 to 52% and endothelin 3 to 96%. The assay had minimal cross reactivity with big endothelin (7%) and no cross reactivity with ANP, AVP, angiotensin II or ACTH.

Arginine vasopressin (AVP) determination

Plasma AVP was measured by RIA following bentonite extraction as described by Skowsky, Rosenbloom and Fisher [14]. In a typical assay, 1 ml of plasma was extracted with bentonite (3 mg), and the AVP bound to the bentonite was eluted using acidified acetone. The eluate was dried under nitrogen. The AVP-containing residue was reconstituted and assayed by RIA. In the RIA, an aliquot of the reconstituted material was mixed with rabbit anti-AVP and incubated for 72 hours at 4°C. [^{125}I] AVP was added, and the incubation was continued for another 24 hours. Bound/free separation was achieved using a second antibody (goat antirabbit gamma globulin). Extraction efficiency was monitored routinely, and the final results were corrected for extraction efficiency (70%). The sensitivity of the assay is 1 pg/ml. All samples were assayed in a single session. The intra-assay variation of the assay is 9%.

Atrial natriuretic peptide (ANP) determination

Plasma samples were extracted using Sep-Pak column as described by Yandle et al [15]. The antibody used in the assay recognizes the amino-terminal end of the ANP molecule [16]. In a typical assay 1 ml of plasma was acidified with 0.1 ml of 1 N HCl, and the mixture was loaded onto a C_{18} Sep-Pak column. The ANP bound to the column was eluted with 80% methanol in triethanolamine buffer (vol/vol), pH 4.0. The eluate was then dried under nitrogen and the residue reconstituted in RIA buffer (pH 7.1, containing 0.01 M sodium phosphate, 0.85% sodium chloride, 0.05 M EDTA and 0.05% bovine serum albumin). The ANP-containing solution was mixed with rabbit anti-ANP and incubated for 24 hours at 4°C. [^{125}I] ANP was added and the incubation was continued for an additional 48 hours. At the end of the incubation, a second antibody (goat antirabbit gamma globulin) was added to separate the free from bound. The extraction efficiency of the assay was 75%. The intra-assay variation of this test is 8.4%, and the assay is sensitive to 10 pg/ml. All samples were assayed in a single session.

Statistical analyses

Data are presented as mean ± SEM. Multiple measure analysis of variance (ANOVA), Duncan's multiple range test and regression analysis were used in evaluation of the data. *P* values equal to or less than 0.05 were considered significant.

Results

Plasma EPO

Data are depicted in Figure 1. Plasma concentration of EPO in group A animals climbed to a peak 24 hours after exposure to hypobaric conditions. Thereafter, EPO concentration declined sharply returning to the baseline values on day 7 despite persistent exposure to hypoxia through day 24. There was a slight and transient fall in EPO level below the baseline values shortly after restoration of normobaric conditions.

Hematocrit

Data are depicted in Figures 2 and 3. Group A animals exhibited a steady rise in hematocrit during the 24 day period of

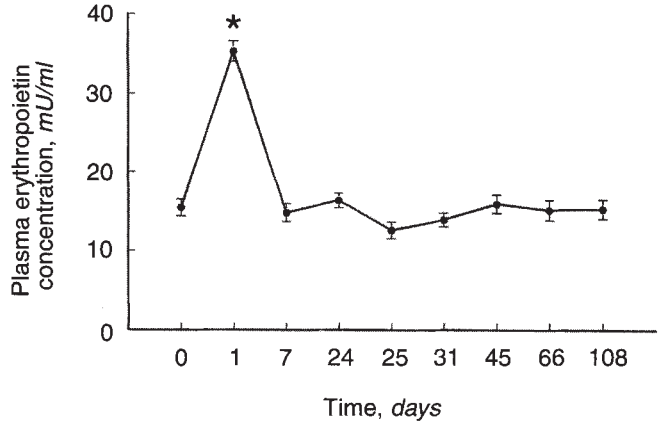

Fig. 1. *Plasma erythropoietin concentration at baseline (time 0) and during the hypoxic (days 1 to 24) and post-hypoxic (days 25 to 108) periods.* Data are given as mean ± SEM, $N = 9$. *$P < 0.001$ relative to baseline value (ANOVA and Duncan's multiple range test).

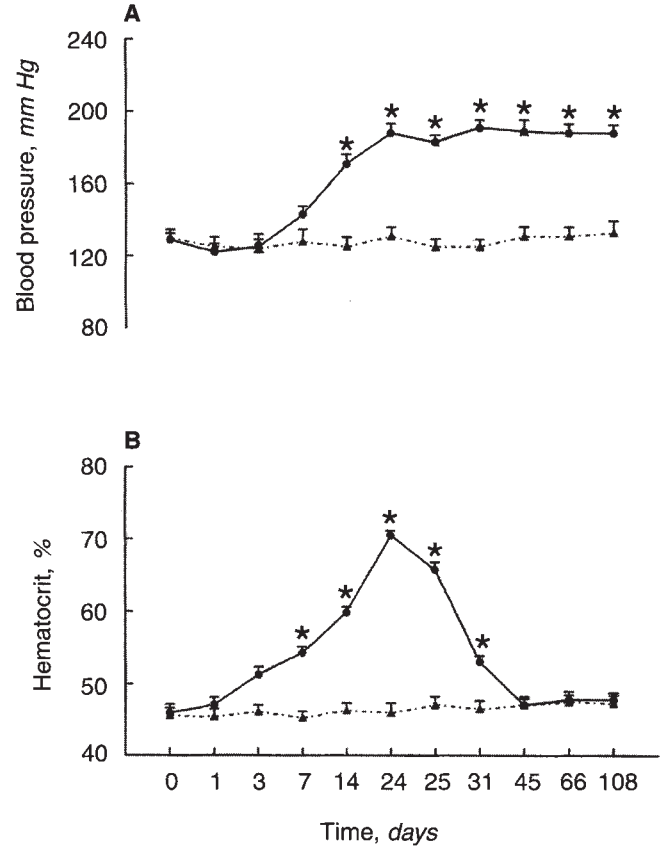

Fig. 2. *Changes of (A) arterial blood pressure and (B) hematocrit at baseline (day 0) and during the hypoxic (days 1 to 24) and post-hypoxic (days 25 to 108) periods.* Data given as mean ± SEM, $N = 10$ in each group. Symbols are: (—●—) hypoxia; (--△--) control; *$P < 0.001$ versus baseline value (ANOVA and Duncan's multiple range test).

exposure to hypobaric conditions. The increase in hematocrit attained statistical significance on day 7 and reached a peak on day 24. This was followed by a steady decline in hematocrit during the normobaric phase of the study, reaching the baseline values on

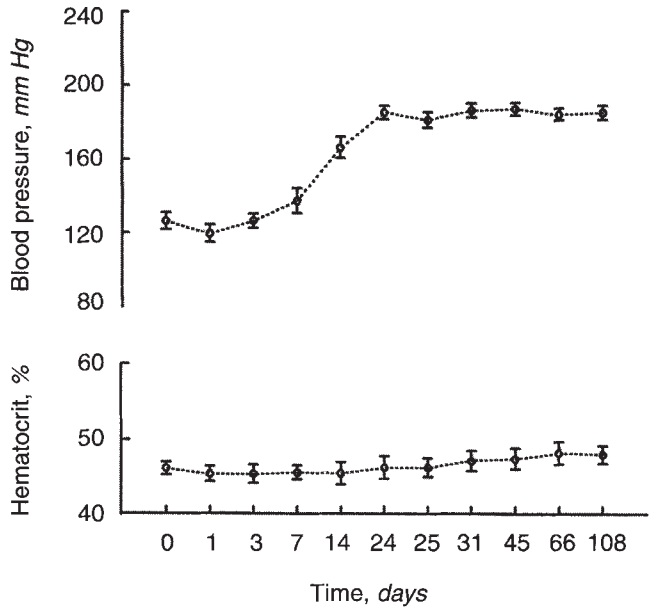

Fig. 3. *Hematocrit and arterial blood pressure in the hypoxic group subjected to regular phlebotomies to keep hematocrit from rising.* Data are given as mean ± SEM ($N = 10$) for the baseline (day 0), hypoxic (days 1 to 24) and post-hypoxic (days 25 to 108) periods. *$P < 0.001$ versus baseline value (ANOVA and Duncan's multiple range test).

day 45. As expected, the hematocrit remained virtually constant in the sham-treated control animals. Likewise, by design, hematocrit remained unchanged in the hypoxic group B animals that were subjected to regular phlebotomies.

Blood volume

Data are shown in Figure 4. Blood volume measurement obtained at the end of the 24-day hypoxic phase in group A animals was significantly greater than that of the sham-treated counterpart. However, repeat measurements obtained on day 66 revealed equal values in the two groups. The observed rise in the blood volume in group A animals after 24-day exposure to hypoxia was exclusively due to the expansion of erythrocyte mass. In fact, plasma volume remained virtually unchanged during the observation period in the study groups.

Blood pressure

Data are illustrated in Figures 2 and 3. Arterial blood pressure remained steady through day 3 of hypobaric hypoxia. It began to progressively rise thereafter reaching a peak on day 24 of hypobaric experience. The rise in arterial blood pressure during the hypoxic phase of the study closely paralleled the rise in hematocrit in group A animals. A significant correlation was found between changes in arterial blood pressure and hematocrit ($r = 0.81$, $P < 0.005$) during this period in group A (Fig. 5). Contrary to our expectation, blood pressure remained elevated throughout the study period despite restoration of normoxia beyond day 24 and subsequent normalization of hematocrit and blood volume. No significant change was observed in arterial blood pressure in the sham-treated group during the observation period. Interestingly, the hypoxic animals subjected to regular phlebotomies (group B) exhibited a severe sustained systemic HTN identical to that found

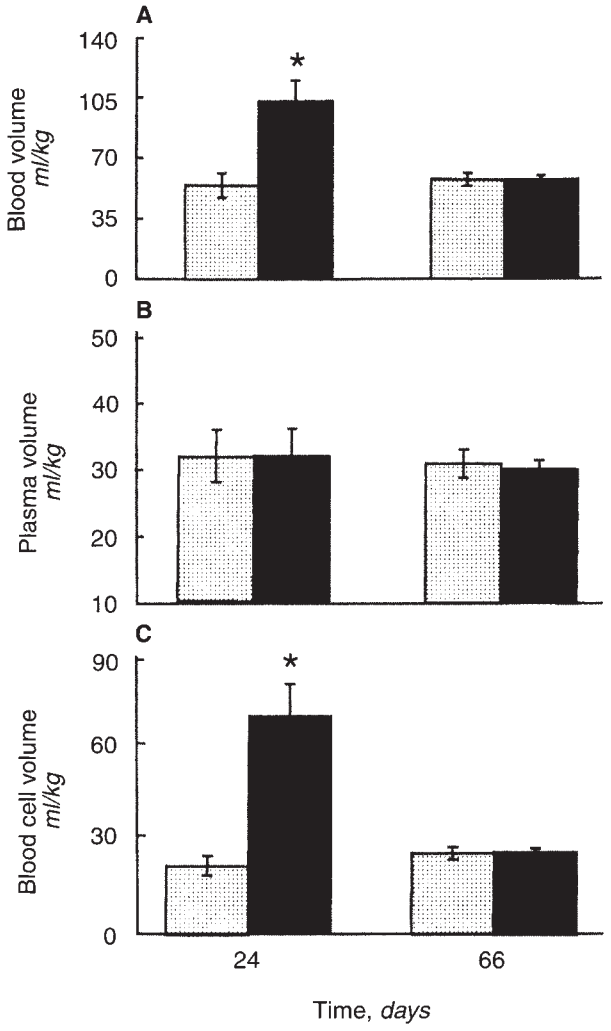

Fig. 4. *(A) Blood volume, (B) plasma volume and (C) blood cell volume at the end of the 24-day hypoxic period (day 24) and several weeks after restoration of normobaric condition (day 66).* Data are compared with those obtained in the sham-treated controls. Data are given as mean ± SEM, $N = 5$ in each group. Symbols are: (□) control; (■) hypoxic; $^*P < 0.01$ versus controls.

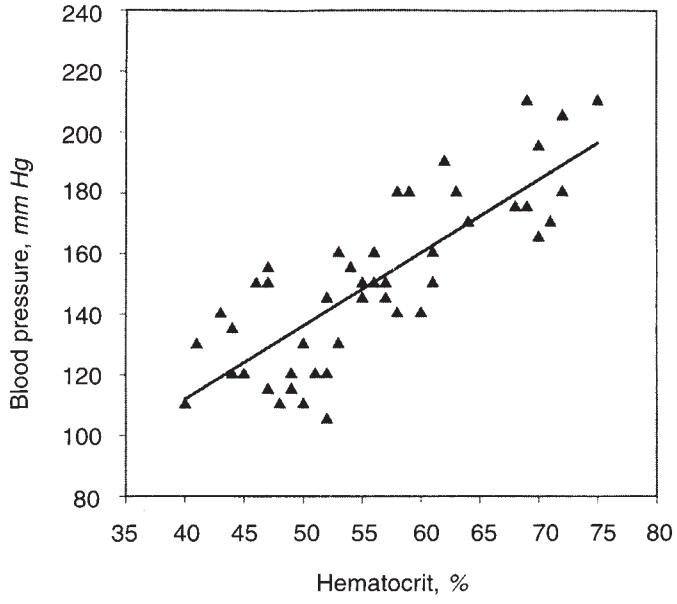

Fig. 5. *Correlation between hematocrit and arterial blood pressure using values obtained at baseline and during the 24-day exposure to hypoxia ($r = 0.81$, $P < 0.005$, $N = 10$).*

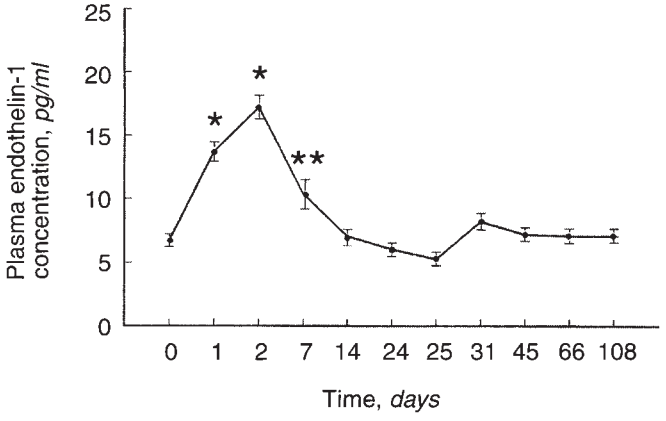

Fig. 6. *Plasma endothelin concentration prior to (day 0), during (days 1 to 24), and after (days 25 to 108) exposure to hypobaric hypoxia.* Data are given as mean ± SEM, $N = 10$. $^*P < 0.001$, $^{**}P < 0.05$ versus baseline value.

in their group A counterparts despite lack of increased hematocrit. These observations clearly suggest that the systemic HTN observed with prolonged hypoxia is not due to the associated rise in hematocrit.

Plasma vasoactive hormones

Plasma endothelin concentration rose significantly reaching a peak on day 2. This was followed by a gradual decline toward the baseline values by the end of the hypoxic period. Subsequent measurements obtained during the post-hypoxic period were not significantly different from the pre-hypoxic baseline values (Fig. 6).

Exposure to hypoxia resulted in a steady rise in plasma ANP concentration reaching a peak by day 7. Thereafter, plasma ANP level gradually declined to a new plateau which was significantly above baseline level (Fig. 7).

Plasma AVP rose insignificantly early in the course of hypoxia. Thereafter, the AVP level returned to baseline where it remained throughout the course of the observation period (Fig. 8).

Discussion

Animals maintained under hypoxic condition exhibited a marked but transient rise in plasma erythropoietin concentration, reaching its peak within 24 hours. This was followed by a gradual rise in hematocrit beginning on day 3, and reaching a peak at the conclusion of the hypoxic phase on day 24. The gradual rise in hematocrit was accompanied by a sharp fall in plasma EPO to the baseline level by day 7. Thus, the increase in the oxygen carrying capacity occasioned by the rise in erythrocyte mass must have served to offset the effect of reduced oxygen tension on EPO production. Accordingly, plasma EPO concentration returned to

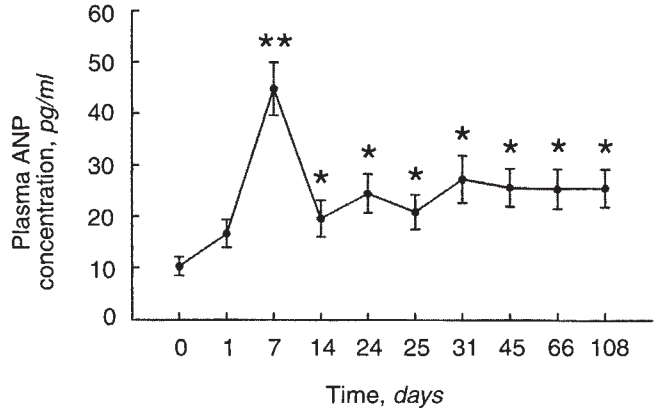

Fig. 7. *Atrial natriuretic peptide (ANP) prior to (day 0), during (days 1 to 24), and after (days 25 to 108) exposure to hypobaric hypoxia.* Data are given as mean ± SEM, $N = 10$. $^*P < 0.001$, $^{**}P < 0.05$ versus baseline value.

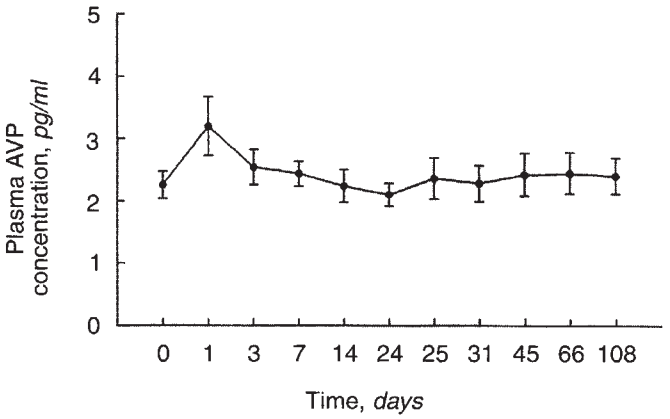

Fig. 8. *Arginine vasopressin (AVP) prior to (day 0), during (days 1 to 24), and after (days 25 to 108) exposure to hypobaric hypoxia.* Data are given as mean ± SEM, $N = 10$.

and remained at baseline level for the remainder of the hypoxic phase in the face of rising hematocrit.

The rise in hematocrit was associated with a marked rise in blood volume along with a parallel and simultaneous rise in blood pressure during the hypoxic phase reaching a peak on day 24. As expected, following the restoration of normal oxygen tension beyond day 24, hematocrit declined steadily returning to the baseline value by day 45. Interestingly, despite the decline in the hematocrit and blood volume to baseline, blood pressure remained severely elevated throughout the remainder of the 108-day observation period.

The parallel rises in hematocrit and arterial blood pressure during the hypoxic phase suggested a possible causal relationship between the two processes. This was thought to be due to the hypoxia-induced increase in erythrocyte mass, expansion of blood volume and the rise in erythrocyte concentration leading to increased blood viscosity and hence total vascular resistance. Thus, the associated changes in both components of blood pressure; that is, circulating volume and vascular resistance were thought to support the observed rise of blood pressure in the presence of an, otherwise, intact cardiovascular system. In an attempt to test the validity of this construct, we sought to dissect the possible role of hypoxia from that of the associated expansion of erythrocyte mass and concentration. To this end we repeated the experiments in a group of animals that were subjected to hypobaric condition as in group A, but whose hematocrit was kept constant by regular phlebotomies gauged to keep hematocrit from rising. To our surprise these animals exhibited a blood pressure rise which was virtually identical in pattern and magnitude to that seen in the original group. This observation clearly demonstrated that the observed HTN was mediated by a hematocrit-independent mechanism. In an attempt to exclude the possible effect of recurrent stress associated with phlebotomies, we have repeated these experiments in animals with dietary iron deficiency and have found identical results (data not shown).

The possible direct contribution, if any, of the endogenous EPO, *per se*, to the pathogenesis of the observed systemic HTN is tenuous. First, the rise in plasma EPO was confined to the early phase of the hypoxic period preceding the onset of systemic HTN. In fact, the EPO levels were at or below the basal levels during the remainder of hypoxic and post-hypoxic periods when systemic HTN was fully expressed. Moreover, exogenous EPO-induced HTN is readily reversed with discontinuation of therapy. In contrast, HTN persisted indefinitely after the transient rise in endogenous EPO production in animals employed here. These observations tend to strongly argue against the direct role of endogenous EPO in the pathogenesis of the sustained systemic HTN in the study animals. Likewise, the observations made in the phlebotomized group tend to exclude the indirect role of EPO through its erythropoietic action.

Based on the above observation, neither endogenous EPO nor the rise in hematocrit seemed to play a central role in the pathogenesis of the observed hypoxia-induced systemic HTN. We thus sought to examine the changes of several vasoactive hormones in the course of the study period to search for the possible mechanism(s).

Rats exposed to hypobaric hypoxia showed a threefold increase in plasma endothelin level by day 2. While values began to decline thereafter, they did not reach the baseline concentrations until the end of the hypoxic period on day 24. Interestingly, however, the onset of HTN on day 7 did not correspond with the peak endothelin level which occurred on day 2. Thus, the role of hypoxia-induced elevation of endothelin in the genesis of the associated systemic HTN is unclear. The rise in plasma endothelin observed in rats exposed to hypobaric hypoxia is consistent with a twofold rise in plasma endothelin reported in a group of normal volunteers upon ascent from 490 m to a high altitude of 4559 m corresponding with the onset of acute pulmonary HTN [17]. Likewise, chronic hypoxia has been shown to increase pulmonary tissue endothelin-1 and ET-A and ET-B receptor gene expressions [18]. In addition, ET-A receptor antagonist has been shown to abrogate acute hypoxia-induced pulmonary HTN in rats [19]. These observations suggest that local induction of endothelin by hypoxia in the lungs may mediate the associated pulmonary HTN. The available data do not allow a definitive conclusion as to the role of endothelin in the genesis of hypoxia-induced sustained systemic HTN observed in the present study. Further studies employing ET-A receptor antagonist are planned to address this issue in the present model.

Animals exposed to hypoxia showed a more than fourfold rise in plasma ANP concentration by day 7. Although the ANP level

declined from the peak during the remaining course of the hypoxic period, it plateaued at a significantly higher level than the baseline value. These observations suggest that the sustained systemic HTN in this model is not due to ANP deficiency. Earlier studies have revealed a rise in plasma ANP in man and perfused ventricular tissues of rats with acute hypoxia [20, 21]. The present study confirms these observations and extends the inquiry beyond the acute phase to long-term hypoxia and post-hypoxic phase in this model.

Plasma AVP concentration rose insignificantly on day 1 and returned to baseline where it remained throughout the course of the hypoxic and post-hypoxic periods. Based on these observations, AVP does not appear to play a major role in the pathogenesis of the sustained systemic HTN in the present model. Interestingly, acute hypoxia has been shown to increase circulating AVP levels in fetal sheep [22]. The hypoxia-stimulated rise in AVP is considered to play a role in ameliorating oxygen delivery and gas exchange during fetal hypoxia [23].

Earlier studies have revealed increased circulating catecholamine levels in response to acute hypoxia [24–26]. The associated hypercatecholaminemia has been shown to subside with the restoration of normal oxygen tension in the acute setting. While unlikely, given the long duration of hypoxia and occurrence of systemic HTN in our animals, we wondered if catecholamines may be elevated during the established phase of HTN in this model. The measurements obtained several weeks following the restoration of normoxia revealed normal catecholamine levels in these hypertensive animals (data not shown). Thus, while increased catecholamines may have, in part, contributed to the genesis of the systemic HTN during the hypoxic phase, hypercatecholaminemia does not appear to be involved in the maintenance of HTN during the post-hypoxic phase.

The rise in endothelin and catecholamine levels can potentially contribute to the occurrence of systemic HTN during the hypoxic phase. However, these changes generally disappear following the restoration of normoxia. Thus, the reason for persistence of HTN following restoration of normoxia is unclear. However, elevations of endothelin and catecholamines along with hemodynamic stress and other events during the extended hypoxia may have caused structural changes to support sustained HTN beyond resolution of the original stimulus. The notion that secondary structural remodeling in response to the potentially reversible primary hemodynamic disturbances can lead to persistent HTN has been widely implicated in the pathogenesis of certain forms of idiopathic and acquired HTN [27, 28].

The fact that chronic hypoxia can cause systemic HTN is not entirely surprising, since hypoxia is known to cause acute and chronic HTN in the pulmonary circulation [29–32]. Acute alveolar hypoxia is known to cause pulmonary vasoconstriction leading to acute pulmonary HTN in both human and experimental animals. The associated pulmonary HTN and vasoconstriction are readily reversed by restoration of normoxia. In contrast to acute hypoxia, persistent hypoxia frequently results in chronic irreversible pulmonary HTN associated with fibrosis and vascular remodeling in humans and experimental animals. The latter is marked by medial hypertrophy of the small muscular arteries and muscularization of the normally nonmuscular arteries [32].

In contrast to pulmonary HTN that occurs shortly after the onset of hypoxia, systemic blood pressure began to rise several days after the onset of hypoxia in our animals. Therefore, systemic HTN could have been readily missed in the course of short-term experiments. Rapid occurrence of pulmonary HTN and delayed occurrence of systemic HTN with hypoxia point to differences in local factors and susceptibilities of the two vascular beds. For instance, hypoxia has been shown to markedly raise the lung content of substance P, a tachykinin possessing potent pulmonary vasoconstrictive property. In fact, pretreatment with tachykinin inhibitor, capsaicin, has been shown to mitigate hypoxia-induced pulmonary HTN in experimental animals [33]. In addition, chronic hypoxia appears to severely impair nitric oxide production by pulmonary artery but not systemic arteries [34, 35]. These observations have led to the general conclusion that chronic hypoxia causes pulmonary but not systemic HTN. In addition to the above studies in experimental animals, several experimental and epidemiological studies in humans residing at high altitudes have failed to show systemic HTN [26, 36–38]. For instance, according to one report, individuals residing in Pikes Peak (4300 m above sea level) for longer than two months had normal systemic arterial blood pressure [36]. Likewise, the adapted natives and newcomers to high altitudes have been found to be normotensive [37] and to have normal plasma and urinary catecholamine levels [26]. It should be noted, however, that large scale longitudinal human studies are presently lacking to address the issue with certainty.

In contrast to the above studies that suggest that chronic hypoxia may not cause systemic HTN, rats employed in the present study showed a steady rise in systemic blood pressure within one to two weeks of exposure to severe chronic hypobaric hypoxia. In fact, HTN persisted indefinitely during the post-hypoxic period. While the preponderance of available studies point to the primary effect of hypoxia on pulmonary but not systemic arterial pressure, a reversible rise in systemic arterial blood pressure has been demonstrated upon the ascent to high altitudes in humans [25, 39–42, 44]. The latter observations along with the findings of the present long-term animal study clearly document that the effect of hypoxia on blood pressure is not confined to the pulmonary circulation and can, in fact, involve the systemic circulation as well. The clinical implication of hypoxia-induced systemic HTN is uncertain. It is not clear if this phenomenon is species specific or if it is operative in the pathogenesis of the complications of sleep apnea, a condition marked by intermittent hypoxia and a high incidence of pulmonary and systemic HTN [43–45]. Further studies are needed to elucidate the factors involved in the pathogenesis of the sustained HTN caused by chronic hypobaric hypoxia in this model.

In conclusion, rats exposed to chronic hypobaric hypoxia exhibited severe systemic HTN that persisted long after the restoration of normobaric condition. We have thus found a model of acquired sustained systemic HTN in genetically normotensive rats. This model can be employed in the studies of the pathophysiology and treatment of systemic HTN.

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